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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/786,998	PACCIARINI ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14 and 18-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-14 and 18-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 10/22/2009 has been received, entered and carefully considered. The following information has been made of record in the instant amendment:

1. Claims 1-12 and 15-17 have been canceled.

2. Claims 13-14, 18-19, 26 and 31-33 have been amended. Claims 14 and 20-30 have been amended to recite 'The method' instead of 'A method'.

4. Remarks drawn to claim objections and rejections under 35 USC 112, second paragraph and 103(a) and Exhibits 1-6.

The following have been overcome:

5. The objection to claim 13 has been overcome by reciting the expansion for the notation MMDX.

6. The rejection of claims 18 and 19 for the lack of recitation of the frequency of administration in the claims has been overcome by amendment. The said claims now recite 'every 4 weeks' for the frequency of administration.

Just a note: Claim 25 depends from claim 26 (a higher numbered claim). The dependency should be changed to a lower numbered claim.

Claims 13-14 and 18-33 are pending in the case.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 is drawn to the method of claim 18 and recites the same duration and frequency of administration for MMDX as in claim 18. Claim 24 should be cancelled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Claims 13-14 under 35 U.S.C. 103(a) as being unpatentable over Bargiotti et al (US 5,304,687, of record) in view of Kuhl et al (Cancer Chemother. Pharmacol., 1993, 33, 10-16, of record), Nakamura et al (Gan. To Kagaku Ryoho 1988, Aug. 15 (8 Pt 2), 2562-7, English Abstract, of record) is being maintained for reasons of record and is reiterated below.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Bargiotti et al, drawn to morpholino derivatives of anthracyclines teach methoxy morpholino doxorubicin (col. 1, lines 10-62; compounds A4 and A5). These derivatives are shown to inhibit solid tumors such as human carcinoma with intravenous and oral route (col. 11, lines 62-68; col. 12, Table 6). Pharmaceutical compositions of the active agent are also taught (col. 5, lines 20-27).

Kuhl, drawn to doxorubicin derivatives, teaches that the methoxymorpholino derivative of doxorubicin (MMDX) has a broad-spectrum antitumor activity and is non-cross-resistant in multi drug tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent (Abstract, page 10). Kuhl also teaches compositions of MMDX and doxorubicin in ethanol (page 11, left column, under Materials and Methods). However, both Bargiotti and Kuhl do not teach or suggest a composition comprising MMDX and an agent like iodized oil.

Nakamura et al teach that intra-arterial infusion of lipiodol (iodized oil) and Adriamycin (same as doxorubicin) showed remarkable therapeutic effects for advanced cancer (English abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising MMDX and iodized oil since compositions comprising the individual active agents have been taught in the prior art to be useful for treatment of tumors. It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

Claims 18-33 as amended now are rejected under 35 U.S.C. 103(a) as being unpatentable over Bargiotti et al (US 5,304,687) in view of Kuhl et al (Cancer Chemother. Pharmacol., 1993, 33, 10-16), Nakamura et al (Gan. To Kagaku Ryoho 1988, Aug. 15 (8 Pt 2), 2562-7, English Abstract) and Gorbunova (Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver, 1990), all of record and Brem et al (US 5,626,862) newly cited.

Bargiotti et al, drawn to morpholino derivatives of anthracyclines teach methoxy morpholino doxorubicin (col. 1, lines 10-62; compounds A4 and A5). These derivatives are shown to inhibit solid tumors such as human carcinoma with intravenous and oral route (col. 11, lines 62-68; col. 12, Table 6). However, the intrahepatic route of administration and the administration of the drug for the time and frequency as recited in instant claims 24 and 25 are not specifically taught.

Kuhl, drawn to doxorubicin derivatives, teaches that the methoxymorpholino derivative of doxorubicin (MMDX) has a broad-spectrum antitumor activity and is non-cross-resistant in

multi drug tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent (Abstract, page 10). This means that methoxymorpholino doxorubicin can be used for the treatment of liver tumor/cancer and can be administered by intravenous infusion as taught by Bargiotti.

Nakamura et al teach that intra-arterial infusion of lipiodol (iodized oil) and Adriamycin (same as doxorubicin) showed remarkable therapeutic effects for advanced cancer (English abstract).

Gorbunova teaches in general that intra hepatic arterial infusion chemotherapy allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor (English abstract). Based on the teaching of Nakamura and Gorbunova one of ordinary skill in the art will recognize that methoxymorpholino doxorubicin in combination with lipidol (iodized oil) can be used for treating liver tumor/cancer via hepatic arterial infusion.

However, the prior art above does not expressly teach administration of the drug for the time period and frequency such as MMDX is administered as an infusion of from about 15 minutes to about 30 minutes every 4 weeks or is administered as a 5-10 minute bolus every 8 weeks.

Brem et al. teach a delivery of chemotherapeutic agents for treating tumors generally. Brem et al. teach that pulse or short term infusions of chemotherapeutic agents are better than continuous infusions (col. 1, lines 38-42). Adriamycin (a closely related doxorubicin) has been suggested for administration for a period of at least a month (col. 7, line 65 and col. 8, lines 24-25). Even though this is with respect to Glioma this teaching of short term infusions and the time period can be applied to treatment of liver tumors and cancers. The time period for short term

infusion and frequency can be optimized for maximum beneficial effects and is well within the skill level of the artisan.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising methoxymorpholino doxorubicin with iodized oil and use the same in a method of treating a human liver tumor and reducing systemic exposure as instantly claimed since such is seen to be taught in the prior art. It is well within the purview of one of ordinary skill in the art to adjust dosages and the frequency of administration based on that taught in the prior art.

One of ordinary skill in the art would have been motivated to use MMDX in hepatic artery administration since prior art recognizes that hepatic artery administration of doxorubicin is beneficial in treating tumor and reducing systemic exposure. Hepatic arterial administration also creates super high concentrations in the organ affected. This localized administration is beneficial for reducing systemic exposure and reducing tumor volume in the liver. One would also make a composition comprising MMDX and lipiodol (iodized oil) since lipiodol in combination with Adriamycin has shown remarkable therapeutic effects for advanced cancer as taught by Nakamura. Hence it is logical to make a composition comprising MMDX and lipiodol since MMDX is structurally close to Adriamycin and has broad spectrum antitumor activity.

Response to Applicants Arguments

Applicants have traversed the rejection of Claims 13-14 under 35 U.S.C. 103(a) arguing that:

1. MMDX (methoxymorpholino doxorubicin) is a new type of anti-tumor drug relative to Adriamycin and has a completely different mechanism of action than Adriamycin (Exhibit 5). They are two different chemical entities. MMDX has the bulky methoxymorpholino group in place of the primary amino group in position 3' of the sugar moiety. The activity of Adriamycin is due to its stimulation of DNA Topoisomerase II cleavage. On the contrary the cytotoxic effects of MMDX are not related to Topoisomerase II inhibition (Exhibit 1). MMDX interacts with DNA Topoisomerase I and stimulates DNA Topoisomerase I-induced cleavage at specific DNA sites (Exhibits 2-4).

2. Applicants quote a passage from Jacques et al, Cancer Surveys, 1993, 17, 219-52, at page 229 (applicants mention that page 229 is to be provided in due course; see page 8 of applicants remarks) according to which, the hepatic intrarterial administration of idarubicin and iododoxorubicin could result in a systemic exposure to active and toxic metabolites, as already shown for doxorubicinol in patients with hepatoma. The desired tumor selectivity could be minimal. This is a teaching away from hepatic intra-arterial administration of MMDX. MMDX (spec. page 2) is converted in vivo into a metabolite having an activity and toxicity 10-fold higher than that of the parent compound.

3. The present invention surprisingly recognizes that hepatic intra arterial administration of MMDX to a patient suffering from liver tumor reduces the amount of MMDX needed by other administration routes and thus reducing systemic exposure to toxic metabolites of MMDX.

Applicants' arguments and the Exhibits provided have been considered but are not found to be persuasive.

1. MMDX may have a different mechanism of action compared to Adriamycin. The mechanism of action, even though relevant, does not lend a patentable distinction. Kuhl, drawn to doxorubicin derivatives, teaches that the methoxymorpholino derivative of doxorubicin (MMDX, as instantly claimed) has a broad-spectrum antitumor activity and is non-cross-resistant in multi drug tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent. The fact that MMDX shows potent antitumor activity is the important teaching in the prior art. One of ordinary skill in the art, knowing that MMDX can be used for treating liver tumors, will use it for the same purpose irrespective of the mechanism by which it operates.

2. Jaques et al (applicants' argument #2 above) mentions about the metabolites of idarubicin and also suggests a possibility of systemic exposure. Jaques et al refer to an equation 1 in their teaching. Applicants have not included equation 1 in their citation. In the absence of equation 1 and the reference (applicants have mentioned that it will be provided in due course. The Examiner did not have the said reference for review) it is not clear in what context the cited passage and equation 1 are mentioned by Jaques. Moreover, the possibility that the desired tumor selectivity could be minimal may be because of the tumor being at a location other than the liver. The passage cited by the applicants does not mention anything regarding the location of the tumor. If the tumor is in the liver then one of ordinary skill in the art would expect administration of MMDX into the hepatic artery to produce high concentrations of the active agent or its metabolite to the tumor. This is taught by Bagriotti and Kuhl. Applicants have stated that MMDX (spec. page 2) is converted in vivo into a metabolite having an activity and toxicity 10-fold higher than that of the parent compound. The specification, at page 2, lines 17-19, teaches

that the reduced derivative of MMDX (the reduced derivative of MMDX is the one wherein the carbonyl group is reduced to an OH) maintains activity in vitro and in vivo at doses 10 fold higher as compared to the parent drug. This teaching doesn't mean that the metabolite's toxicity is ten fold higher. The paragraph at which this teaching appears, mentions about the antitumor activity of anthracyclines and in this context, the reference to the activity means its antitumor activity and not its toxicity.

3. Based on the teachings of Bagriotti and Kuhl one of ordinary skill in the art would expect administration of MMDX into the hepatic artery to produce high concentrations of the drug in the tumor that is located in the liver because of the proximity of the site of administration of the MMDX and the location of the tumor. The re is a reasonable expectation of success.

Applicants have traversed the rejection of claims 18-33 under 35 USC 103(a) arguing that:

1. Their arguments advanced for claims 13-14 above apply to the instant rejection too.

2. Gorbunova and Brem do not teach or suggest the administration of MMDX for the time period and frequency as instantly claimed. According to Gorbunova the time for intrahepatic administration is 72 hours for Adriamycin and 96 hours for 5-fluorouracil. There are also side effects and disadvantages associated with lengthy administration. According to the present invention it is possible to administer MMDX in a much shorter time period.

The counter arguments by the Examiner for claims 13-14 are as above. Gorbunova teaches in general that intra hepatic arterial infusion chemotherapy allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor. Since such an

infusion creates super high concentrations one of ordinary skill in the art will adjust the amount of MMDX to a level that produces maximal beneficial effect and minimal side effects. Such is routine and also well within the skill level of the artisan. Brem et al. teach that pulse or short term infusions of chemotherapeutic agents are better than continuous infusions. This teaching of Brem suggests adjustment of the time of administration. The use of MMDX for treatment of tumor has been taught by Bagriotti and Kuhl. Gorbunova and Brem need not necessarily teach the same. It would have been obvious to one of ordinary skill in the art to use MMDX and adjust its time and frequency of administration without Gorbunova and Brem teaching or suggesting the same. The instant claims are rendered obvious by the prior art of record.

Conclusion

Claims 13-14 and 18-33 are rejected

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/

Supervisory Patent Examiner, Art Unit 1623